(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 881 212 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
02.12.1998 Bulletin 1998/49

(51) Int. Cl.[6]: **C07C 253/30**, C07C 255/62

(21) Application number: **98109211.7**

(22) Date of filing: **20.05.1998**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **26.05.1997 JP 134195/97**

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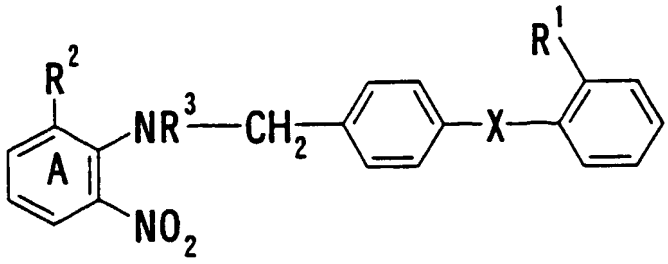
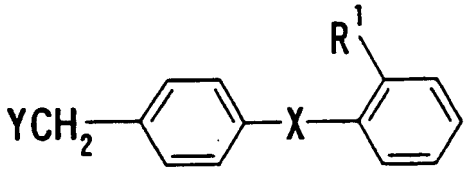
(54) Production method of aminobenzene compound

(57) The present invention is to provide an industrially useful production method of an aminobenzene compound represented by the formula:



which is characterized by reacting a mixture of a mono-halogeno compound represented by the formula:



and di-halogeno compound represented by the formula:

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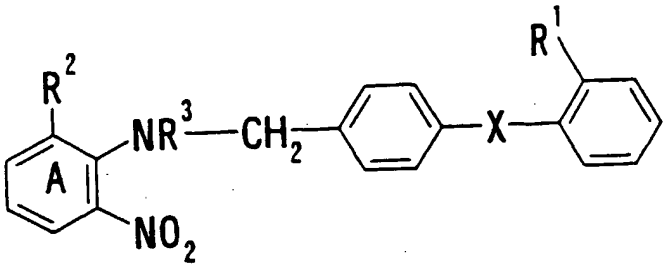
salt thereof represented by the formula (III) [redacted] compound or a salt thereof represented by the [redacted]ula (II') does not react with a compound or a salt thereof represented by the formula (III) and that a compound or a salt thereof represented by the formula (IV) is selectively produced. Moreover, they found that when a compound or a salt thereof represented by the formula (IV) wherein R^3 is hydrogen atom, which is obtained by subjecting a compound or a salt thereof represented by the formula (IV) to hydrolysis reaction with a mineral acid such as hydrochloric acid, etc., is crystallized, a compound or a salt thereof represented by the formula (II') is removed in a mother liquor. Since a compound or a salt thereof represented by the formula (II') which does not react with a compound or a salt thereof represented by the formula (I) is easily removed, a compound or a salt thereof represented by the formula (IV) can be synthesized at a low price, in a good yield and advantageously in view of an industrial production without isolating and purifying a compound or a salt thereof represented by the formula (II), that is, without exposing a compound or a salt thereof represented by the formula (II) to the workers and environment. According to these findings, the present inventors have completed the present invention.

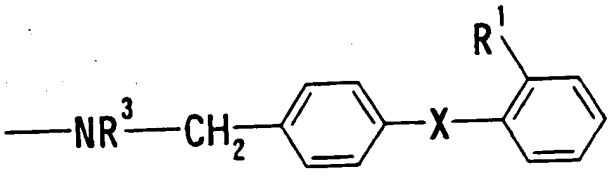
The present invention relates to

(1) a method for producing an aminobenzene compound of the formula (IV):



(IV)

wherein the ring A is a benzene ring which may have an optional substituent in addition to the group R^2, the nitro group and the group of the formula:

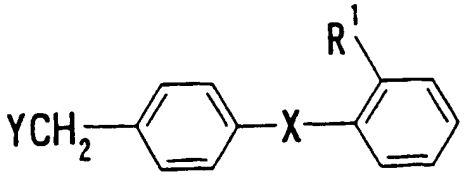


;

R^1 is a group capable of forming an anion or transformable thereinto;
R^2 is a group capable of forming an anion or transformable thereinto;
R^3 is an acyl group; and
X is a chemical bond or a spacer having a chain length of 1 to 2 atoms as the linear moiety between the adjoining phenylene group and phenyl group; or a salt thereof,

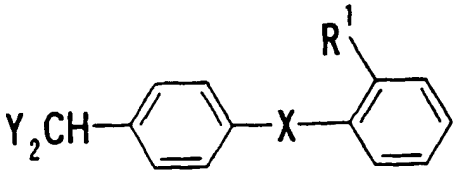
which comprises reacting a mixture containing

(i) a mono-halogeno compound of the formula (II):



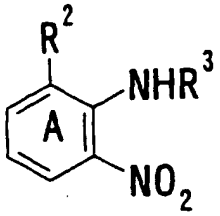
(II)

wherein Y is a halogen atom and the other symbols are as defined above,
or a salt thereof and
(ii) a di-halogeno compound of the formula (II'):



(II')

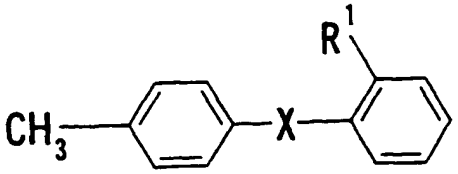
wherein each symbol is as defined above, or a salt thereof with a compound of the formula (III):



(III)

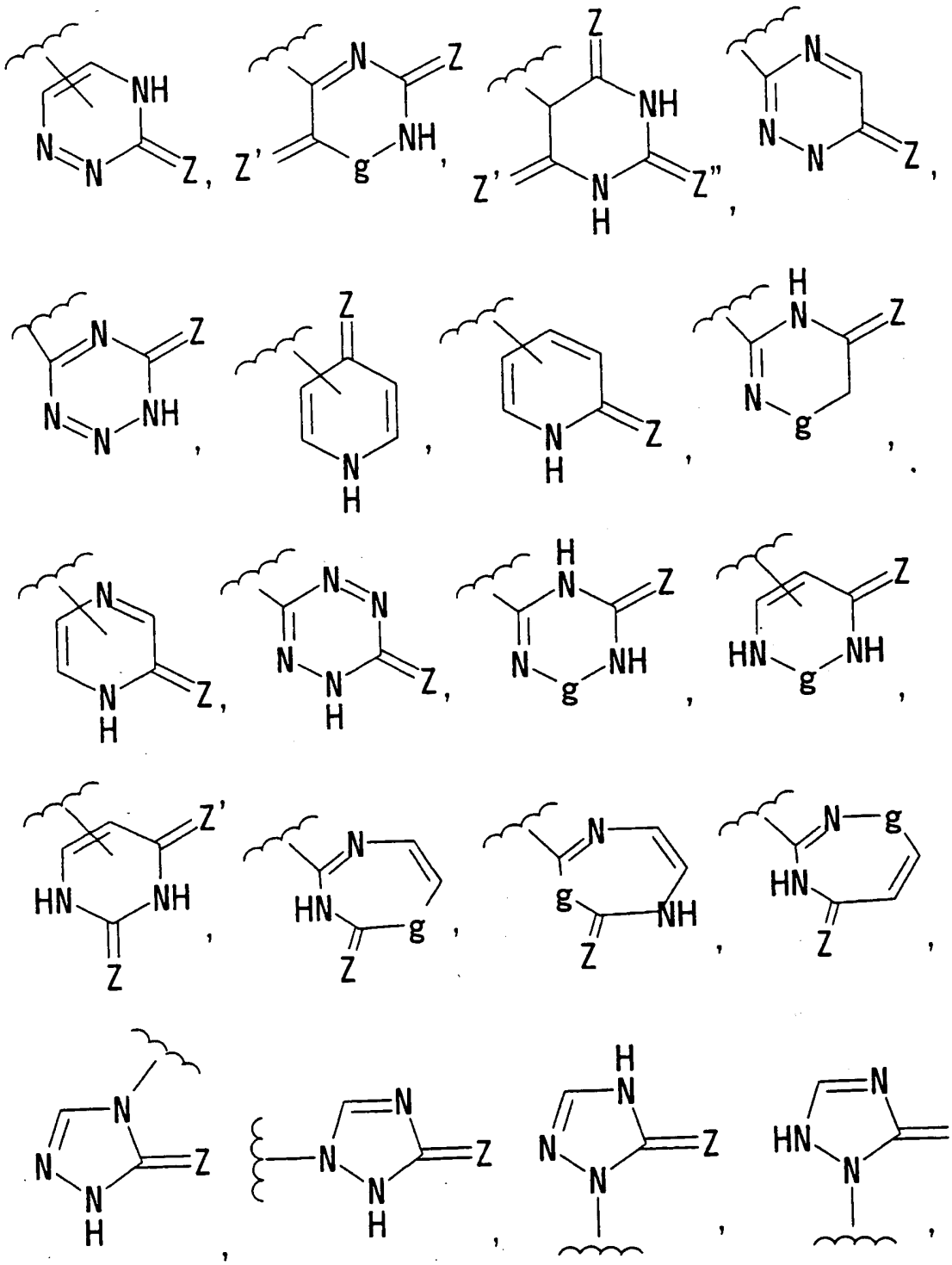
wherein the ring A is a benzene ring which may have an optional substituent in addition to the group R^2, the nitro group and the group of the formula: $-NHR^3$ and the other symbols are as defined above, or a salt thereof;

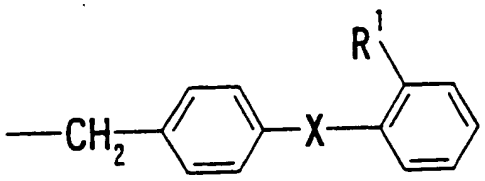
(2) a method of the above (1), wherein said reaction is carried out in acetonitrile;
(3) a method according to the above (1) or (2), wherein the mixture is a reaction mixture which is obtained by subjecting a compound of the formula (I):



(I)

wherein R^1 is a group capable of forming an anion or transformable thereinto; and X is a chemical bond or a spacer having a chain length of 1 to 2 atoms as the linear moiety between the adjoining phenylene group and phenyl group; or a salt thereof to halogenation;
(4) a method of any of the above (1) to (3), wherein Y is a bromine atom;
(5) a method of any of the above (1) to (4), wherein R^1 is (1) a carboxyl group, (2) a tetrazolyl group, (3) a trifluoromethanesulfonamido group, (4) a phosphono group, (5) a sulfo group, (6) a 5-7 membered monocyclic heterocyclic group which contains one or more of N, S and O and which may be substituted;
(6) a method of the above (5), wherein the heterocyclic group is a group of the formula:



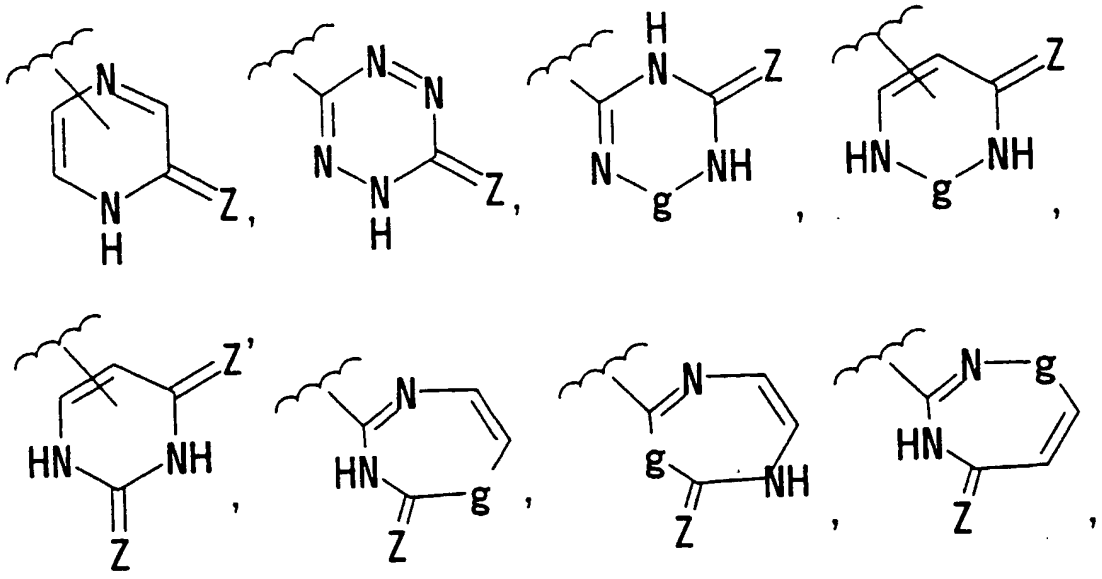


(14) a method of any of the above (1) to (13), wherein R^2 is (1) an optionally esterified or amidated carboxyl group, (2) tetrazolyl group, (3) trifluoromethanesulfonamido group, (4) phosphono group or (5) sulfo group, which may be protected by an optionally substituted lower alkyl group or an acyl group;
(15) a method of any of the above (1) to (13), wherein R^2 is a group of the formula: -CO-D wherein D is an optionally substituted alkoxy group;
(16) a method of any of the above (1) to (13), wherein R^2 is a group of the formula: -CO-D wherein D is (1) hydroxy group or (2) a lower (C_{1-4}) alkoxy whose alkyl moiety may be substituted with hydroxy, amino, halogen, lower (C_{2-6}) alkanoyloxy, lower (C_{3-8}) cycloalkanoyloxy, lower (C_{1-6}) alkoxycarbonyloxy, lower (C_{3-8}) cycloalkoxycarbonyloxy, lower (C_{1-4}) alkoxy or lower (C_{3-8}) cycloalkoxy;
(17) a method of any of the above (1) to (13), wherein R^2 is a methoxycarbonyl group;
(18) a method of any of the above (1) to (17), wherein R^3 is a group of the formula: $-COR^8$ or $-COOR^8$ wherein R^8 is an optionally substituted hydrocarbon residue;
(19) a method of the above (18), wherein R^8 is a lower (C_{1-5}) alkyl or a lower (C_{2-5}) alkenyl group optionally substituted with hydroxy group, amino group, halogen or a lower (C_{1-4}) alkoxy group;
(20) a method of any of the above (1) to (17), wherein R^3 is t-butoxycarbonyl;
(21) a method of any of the above (1) to (20), wherein said reaction is carried out in the presence of potassium carbonate in acetonitrile;
(22) a method of any of the above (1) to (21), wherein said reaction is carried out between (1) a mixture containing 2-(4-bromomethylphenyl)benzonitrile and 2-(4,4-dibromomethylphenyl)benzonitrile and (2) methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate to give methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate;etc.

In the above formulas, Y represents a halogen atom such as F, Cl, Br, I, etc. Among others, a bromine atom is preferable.

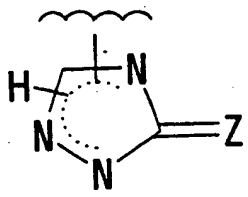
Examples of a group capable of forming an anion (a group having a hydrogen atom capable of leaving as a proton) represented by R^1 in the above formulas include, for example, (1) a carboxyl group, (2) a tetrazolyl group, (3) a trifluoromethanesulfonamido group ($-NHSO_2CF_3$), (4) a phosphono group, (5) a sulfo group, (6) a 5-7 membered (preferably 5-6 membered) monocyclic heterocyclic group which contains one or more of N, S and O and which may be substituted, etc.

Examples of the above a 5-7 membered (preferably 5-6 membered) monocyclic heterocyclic group which contains one or more of N, S and O include, e.g.,

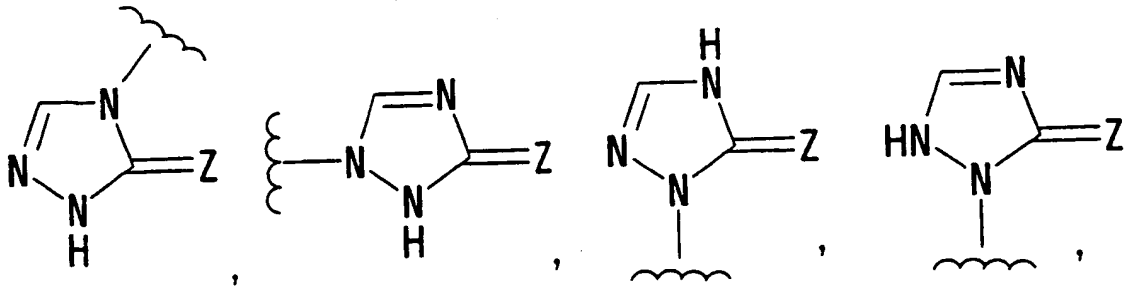


etc.

The chemical bond between the heterocyclic group represented by R^1 and the phenyl group to which said heterocyclic group binds may be a carbon-carbon bond as shown above and a nitrogen-carbon bond via one of the several nitrogen atoms when the symbol g is -NH-, etc. in the above formulas. For example, when R^1 represents

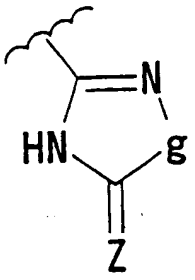


specific examples of said group include

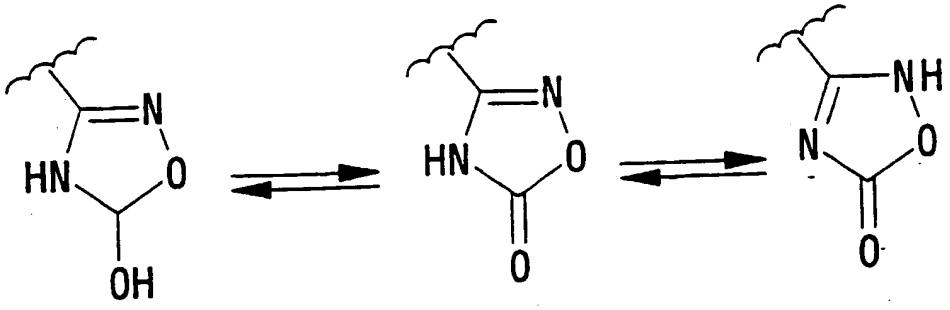


etc.

Other examples binding through the nitrogen atom include

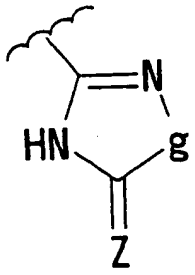


when Z = O, and g = O,



a' b' c'

the above-described three tautomeric isomers a', b' and c' exist.
The heterocyclic group represented by the formula:



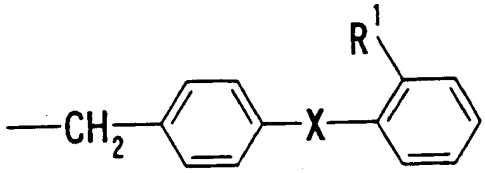
includes all of the above-mentioned a' ,b' and c'.

A group capable of forming an anion as the group R^1 may be protected by an optionally substituted lower (C_{1-4}) alkyl group, acyl group (e.g. a lower (C_{2-5}) alkanoyl, benzoyl, etc.), etc. at any possible position.

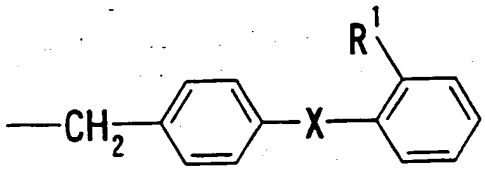
Examples of an optionally substituted lower (C_{1-4}) alkyl group include (1) a lower (C_{1-4}) alkyl group optionally substituted with 1-3 phenyl groups optionally having a halogen atom, a nitro group, a lower (C_{1-4}) alkyl, a lower (C_{1-4}) alkoxy, etc. (e.g. methyl, triphenylmethyl, p-methoxybenzyl, p-nitrobenzyl, etc.), (2) a lower (C_{1-4}) alkoxy-lower (C_{1-4}) alkyl group (e.g. methoxymethyl, ethoxymethyl, etc.), (3) a group of the formula: $-CH(R^4)-OCOR^5$ wherein R^4 is (a) a hydrogen atom, (b) a straight or branched lower C_{1-6} alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), (c) a straight or branched lower (C_{2-6}) alkenyl group or (d) C_{3-8} cycloalkyl group (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.), and R^5 is (a) a straight or branched lower C_{1-6} alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.), (b) a straight or branched lower C_{2-6} alkenyl group, (c) a lower C_{1-3} alkyl group substituted with C_{3-8} cycloalkyl group (e.g. cyclopentyl, cyclohexyl, cycloheptyl, etc.) or an optionally substituted aryl group (e.g. a phenyl or naphthyl group optionally having a

etc.), N-arylamino (e.g. phenylamino, etc.), alicyclic amino (e.g. morpholino, piperidino, piperazino, N-phenylpiperazino, etc.) etc.), (7) a group of the formula: -CO-D' wherein D' is hydroxy group or an optionally substituted lower (C_{1-4}) alkoxy whose alkyl moiety may be substituted with hydroxy group, a lower (C_{1-4}) alkoxy, a lower (C_{2-6}) alkanoyloxy (e.g. acetoxy, pivaloyloxy, etc.), a lower (C_{1-6}) alkoxy-carbonyloxy (e.g. methoxy-carbonyloxy, ethoxy-carbonyloxy, etc.), a lower (C_{3-6}) cycloalkoxycarbonyloxy (e.g. cyclohexyloxycarbonyloxy, etc.), or (8) tetrazolyl, trifluoromethanesulfonamido group, phosphono group, sulfo group, etc. each of which may be protected by an optionally substituted lower (C_{1-4}) alkyl (similar to the "optionally substituted lower (C_{1-4}) alkyl group" exemplified as the protective group for a group capable of forming an anion as the group R^1) or acyl (e.g. a lower (C_{2-5}) alkanoyl, benzoyl, etc.).

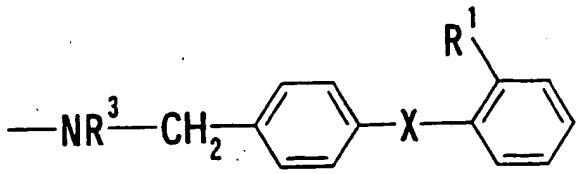
One or two of these substituents may be concurrently present at any possible positions on the benzene ring. As the substituents which the ring A may have in addition to the group R^2, the group of the formula: $-NHR^3$ unsubstituted or substituted with a group of the formula:



and the nitro group, an optionally substituted lower (C_{1-4}) alkyl (e.g. a lower (C_{1-4}) alkyl optionally substituted with hydroxy group, carboxyl group, halogen, etc., etc.), halogen, etc. are preferable and it is more preferable that the ring A in the formula (III) has no substituent in addition to the group R^2, the group of the formula: $-NHR^3$ unsubstituted and the nitro group; and the ring A in the formula (IV) has no substituent in addition to the group R^2, the group of the formula: $-NHR^3$ substituted with a group of the formula:



i.e., the group of the formula:



and the nitro group.

In the above formula, examples of the group capable of forming an anion (a group having a hydrogen atom capable of leaving as a proton) represented by R^2 include, for example, (1) optionally esterified or amidated carboxyl group, (2) tetrazolyl group, (3) trifluoromethanesulfonamido group ($-NHSO_2CF_3$), (4) phosphono group, (5) sulfo group, etc. These groups may be protected by an optionally substituted lower alkyl group (similar to the "optionally substituted lower (C_{1-4}) alkyl group" exemplified as a protective group for a group capable of forming an anion represented by R^1) or acyl group (e.g. a lower (C_{2-5}) alkanoyl, benzoyl, etc.). Any group capable of forming an anion or any group capable of forming an anion or transformable thereinto biologically or physiologically (e.g. through biological reactions such as oxidation, reduction, hydrolysis, etc. caused by enzymes in the body, etc.), or chemically is acceptable.

Examples of an optionally esterified or amidated carboxyl as the group R^2 include a group of the formula: -CO-D wherein D is (1) hydroxy group, (2) an optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-di-lower (C_{1-4}) alkylamino, etc.) or (3) an optionally substituted alkoxy. Specific Examples of said optionally substituted alkoxy include (i) an optionally substituted lower (C_{1-6}) alkoxy group whose alkyl moiety may be substituted with a hydroxy group, an optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-di-lower (C_{1-4}) alkylamino, piperid-

(C_{1-4}) alkylamino, etc.), halogen, a lower (C_{1-4}) alkoxy group, a lower (C_{1-4}) alkylthio group, etc.

Examples of the aralkyl group represented by R^8 include phenyl- lower (C_{1-4}) alkyl, etc. such as benzyl, phenethyl, etc. and examples of the alkyl group represented by R^8 include phenyl, etc.

Each of the above mentioned aralkyl group or aryl group may have, at any possible position of the benzene ring, for example, halogen (e.g. F, Cl, Br, etc.), a nitro group, an optionally substituted amino group(e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-di-lower (C_{1-4}) alkylamino, etc.), a lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, etc.), a lower (C_{1-4}) alkylthio (e.g. methylthio, ethylthio, etc.), a lower (C_{1-4}) alkyl (e.g. methyl, ethyl, etc.), etc.

Among others, as the group R^8, an optionally substituted alkyl or alkenyl group (e.g. a lower (C_{1-5}) alkyl or a lower (C_{2-5}) alkenyl group optionally substituted with hydroxy group, amino group, halogen or a lower (C_{1-4}) alkoxy group, etc.) is preferable and in particular a lower (C_{1-5}) alkyl (more preferably t-butyl) is preferable.

As the salt of a compound represented by the formulas (I), (II), (II'), (III) or (IV), any salts can be employed, unless they disturb the reaction of the present invention. Preferable examples of the salts include a salt with an inorganic base, a salt with an organic base, a salt with an inorganic acid, a salt with an organic acid, a salt with a basic or acidic amino acid, etc. Preferable examples of the salt with an inorganic base include an alkali metal salt such as sodium salt, potassium salt, etc.; an alkaline earth metal salt such as calcium salt, magnesium salt, etc.; aluminum salt; ammonium salt; etc. Preferable examples of the salt with an organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.

Preferable examples of the salt with an inorganic acid include hydrochloride, hydrobromide, nitrate, sulfate, phosphate, etc. Preferable examples of the salt with an organic acid include formate, acetate, trifluoroacetate, fumarate, oxalate, tartarate, maleate, citrate, succinate, malate, methanesulfonate, benzene sulfonate, p-toluene-sulfonate, etc.

Preferable examples of the salt with a basic amino acid include a salt with arginine, lysine, ornithine, etc. Preferable examples of the salt with an acidic amino acid include a salt with aspartic acid, glutamic acid, etc.

When a compound or a salt thereof represented by the formula (I) is subjected to halogenation reaction, a method described in Japanese Patent Laid-open Publication No. 6-192170 or a method similar thereto can be employed. Usually, per mole of a compound or a salt thereof represented by the formula (I), about 1-2 moles of a halogenating agent such as N-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin, N-bromoacetamide, N-bromophthalimide, N-bromomaleimide, N-bromosulfonamide, etc. (preferably N-bromosuccinimide (NBS), 1,3-di-bromo-5,5-dimethylhydantoin, etc.) are used. Said halogenation reaction is preferably carried out in the presence of a radical starting agent such as heat, light, benzoyl-peroxides, azobis compounds, etc. Among others, azobis compounds are preferably employed.

Examples of the azobis compounds include 2,2'-azobis(2,4-dimethylvaleronitrile), 2,2'-azobis(2-methylbutyronitrile), azobisisovaleronitrile, 1,1'-azobis(cyclohexanecarbonitrile), 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile), 2,2'-azobis(2-amidinopropane) hydrochloride, dimethyl-2,2'-azobisisobutyrate, etc. Among others, 2,2'-azobis(2,4-dimethylvaleronitrile), 2,2'-azobis-isobutyronitrile (AIBN) and 2,2'-azobis-(2,4-dimethylvaleronitrile) are preferable, and in particular 2,2'-azobis(2,4-dimethylvalero-nitrile) is preferable. The proportion of said azobis compound is about 0.1-3 % based on the halogenating agent. The preferred proportion is about 2-3 % for 2,2'-azobisisobutyronitrile (AIBN) and about 0.1-0.3 % for 2,2'-azobis(2,4-dimethylvaleronitrile).

Examples of the reaction solvent include halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, etc., ethers such as tetrahydrofuran, dioxane, etc., esters such as ethyl acetate, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., aprotic polar solvents such as dimethylformamide, dimethylsulfoxide, dimethylacetamide, etc., etc. Among others, halogenated hydrocarbons is are preferable and in particular dichloromethane is preferable.

The solvents are preferably used in the amount of about 100-10000 ml per 1 mole of a compound or a salt thereof represented by the formula (I). A mixture containing a compound or a salt thereof represented by the formula (II) and a compound or a salt thereof represented by the formula (II') is produced by stirring the reaction solution at about 20-100 °C,preferably 40-60 °C, for about 1-10 hours, preferably for about 2-6 hours, in the above solvents and the concentrate containing a compound or a salt thereof represented by the formula (II) and a compound or a salt thereof represented by the formula (II') is obtained by adding water to the mixture and concentrating the organic layer. The obtained concentrate is preferably subjected to alkylating reaction with a compound or a salt thereof represented by the formula (III), without isolating and purifying a compound or a salt thereof represented by the formula (II).

In the mixture containing a compound or a salt thereof represented by the formula (II) and a compound or a salt thereof represented by the formula (II'), it is preferable to use about 1/20 to about 1 mole of the compound or a salt thereof represented by the formula (II'), more preferably about 1/16 to 1/4 mole of the compound or a salt thereof represented by the formula (II'), relative to 1 mole of the compound or a salt thereof represented by the formula (II).

Said alkylating reaction of a compound or a salt thereof represented by the formula (III) with a mixture containing a compound or a salt thereof represented by the formula (II) and a compound or a salt thereof represented by the formula (II') is carried out by a method described in Japanese Patent Laid-open Publication No. 4-364171 or a similar method thereto. Usually, about 0.8 - 2 moles of a compound or a salt thereof represented by the formula (III), preferably 0.95-1.1 moles, are used per 1 mole of a compound or a salt thereof represented by the formula (II).

represented by the formula (II) having strong mutagenicity from being exposed to the workers producing said compound and to the environment, and therefore, the production method of the present invention is an industrially advantageous method for producing a compound or a salt thereof represented by the formula (IV).

Furthermore, according to the production method of the present invention, it is industrially advantageous to produce a compound or a salt thereof represented by the formula (IV) since the compound or a salt thereof represented by the formula (IV) can be produced in good yield (which increases 10 % or more, compared with a known production method).

EXAMPLES

The present invention is explained in further detail by the following Working Examples, Comparative Examples and Reference Examples but the present invention is not limited thereto.

Working Example 1

Production of methyl 2-[[(2'-cyanobiphenyl-4-yl)methylamino]-3-nitro-benzoate [MBN]

A mixture of 2-(4-methylphenyl)benzonitrile [MPB] 23 g, NBS 22 g and 2,2'-azobis(2,4-dimethylvaleronitrile) 47 mg was suspended in dichloromethane 44 ml and the mixture was stirred at 45-50 °C for about 5 hours. To the reaction mixture was added water 46 ml and the organic layer was separated. This operation was conducted three times. The organic layer was concentrated and acetonitrile 50 ml was added to the concentrate. The solution was again concentrated and acetonitrile 50 ml was added to the concentrate to give acetonitrile solution of 2-(4-bromomethylphenyl)benzonitrile [BMB] (116 g; Yield based on the theoretical amount of (2-(4-bromomethylphenyl)benzonitrile: 84 %).

To the acetonitrile solution where BMB is mixing with 2-(4-methylphenyl)benzonitrile [MPB] which was not brominated and 2-(4,4-dibromomethylphenyl)benzonitrile which is a compound similar to BMB, was added a mixture of methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate [BAN] 30.1 g, potassium carbonate 40.8 g and acetonitrile 160 ml and the solution was stirred at about 82 °C for about 5 hours to proceed the reaction. The solution was cooled to room temperature and precipitated crystals were filtered off. The filtrate was concentrated to give methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyano-biphenyl-4-yl)methyl]amino]-3-nitrobenzoate [BBN]. The concentrate was dissolved in methanol 190 g. To the methanol solution was dropped concentrated hydrochloric acid 106 g and the solution was heated to refluxing temperature for 2 hours and thereafter stirred under reflux for 2 hours to proceed the reaction. The reaction solution was cooled and the precipitated crystals were filtered and dried to give methyl 2-[N-(2'-cyanobiphenyl-4-yl)methylamino]-3-nitrobenzoate [MBN] 35.1 g (yield based on 2-(4-methylphenyl)benzonitrile [MPB] : 76.1 %).

Comparative Example 1

Production of methyl 2-[[(2'-cyanobiphenyl-4-yl)methylaminol-3-nitro-benzoate [MBN]

A mixture of 2-(4-methylphenyl)benzonitrile [MPB] (30 g), N-bromosuccinimide [NBS] (28.35 g), 2,2'-azobis(2,4-dimethylvaleronitrile) [ABN-V] (60 mg) and methylene chloride (75 g) was stirred at 45-50 °C for 3-4 hours under reflux. The reaction solution was cooled to 38-42 °C and washed with water (60 g) three times. The methylene chloride layer was discolored with activated charcoal (0.15 g) and was concentrated under reduced pressure. To the solution was added crystal seeds (0.01 g). The solution was cooled to not more than 5 °C and crystals were isolated and dried to obtain the first crystals of 4-(2-bromomethylphenyl)benzonitrile [BMB] (25.3 g, 60 %). The second crystals were obtained from mother liquor (5.3 g, 13 %).

To the obtained first and second crystals of BMB (30.6 g) were added a mixture of methyl 2-tert-butoxycarbonylamino-3-nitrobenzoate [BAN] 33.7 g, potassium carbonate 45.5 g and acetonitrile 280 g and the solution was stirred at about 82 °C for about 5 hours to proceed the reaction. The solution was cooled to room temperature and the precipitated crystals were filtered off. The filtrate was concentrated to give methyl 2- [N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate [BBN].

The concentrate was dissolved in methanol 213 g. To the solution was dropped concentrated hydrochloric acid 119 g, and the solution was heated to refluxing temperature for 2 hours and further stirred for 2 hours under reflux to proceed the reaction. The reaction solution was cooled and the precipitated crystals were filtered and dried to give methyl 2-[N-(2'-cyanobiphenyl-4-yl)methylamino]-3-nitrobenzoate [MBN] 27.9 g (yield based on 2-(4-methylphenyl)benzonitrile [MPB] : 66 %).

Working Example 2(2)

Production of methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)-methyl]amino]-3-nitrobenzoate [BBN]

A mixture of methyl 2-t-butoxycarbonylamino-3-nitro benzoate [BAN] (354 kg) obtained in Reference Example 2, acetonitrile solution of 4-(2-bromomethylphenyl)benzonitrile [BMB] obtained in Working Example 2(1) and anhydrous potassium carbonate (475 kg) was added to acetonitrile (1600 kg) and the solution was heated for about 5 hours under reflux (80-85 °C). The reaction solution was cooled and insoluble materials were filtered off and washed with acetonitrile (320 kg). The filtrate and the acetonitrile solution used for washing the insoluble materials were concentrated under reduced pressure to give the concentrate of methyl 2-[N-t-butoxy-carbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitro-benzoate [BBN].

Working Example 2(3)

Production of methyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate [MBN]

The concentrate obtained in Working Example 2(2) (methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitro-benzoate [BBN]) and methanol (3200 L) were mixed, and 35 % concentrated hydrochloric acid (1050 L) was added to the mixture at 30 °C or less for about 4 hours. The mixture was heated to reflux temperature (67-69 °C) at a speed of 10 °C or less/hour, and stirred for about 1.5 hours under reflux. The reaction solution was cooled, to which was added methanol (800 L), and the solution was stirred at 3-10 °C for about 1 hour. The precipitated crystals were separated, washed with methanol and dried to give methyl 2-[[(2'-cyano-biphenyl-4-yl)methyl]amino]-3-nitro-benzoate [MBN] (407 kg; yield based on MPB: 75 %).

m.p. 140-141 °C
^{1}H-NMR (200MHz, DMSO-d_6) δ : 3.84 (3H, s), 4.26 (2H, m), 6.86 (1H, t), 7.46 (2H, d), 7.54-7.65 (4H, m), 7.79 (1H, d), 7.95 (1H, dd), 8.05-8.11 (2H, m), 8.67 (1H, t)

Comparative Example 2(1)

Production and isolation of 2-(4-bromomethylphenyl)benzonitrile[BMB]

A mixture of 2-(4-methylphenyl)benzonitrile [MPB] (30 kg), N-bromosuccinimide [NBS] (28.35 kg), 2,2'-azobis(2,4-dimethylvalero-nitrile) [ABN-V] (60g) and methylene chloride (75 kg) was stirred at 45-50 °C for 3-4 hours under reflux and the reaction solution was cooled to 38-42 °C and washed with water (60 kg) three times. The methylene chloride layer was discolored with activated charcoal (0.15 kg) and concentrated under reduced pressure. To the solution was added crystal seeds (0.01 kg), and the solution was cooled to 5 °C or less. The precipitated crystals were separated and dried to give the first crystals of 4-(2-bromomethylphenyl)benzonitrile [BMB] (28.5 kg, 67 %). From mother liquor was obtained the second crystals (5.3 kg, 13 %).

Comparative Example 2(2)

Production of methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)-methyl]amino]-3-nitrobenzoate [BBN]

A mixture of methyl 2-t-butoxycarbonylamino-3-nitro-benzoate [BAN] (37.2 kg) obtained in Reference Example 2, 4-(2-bromomethylphenyl)benzonitrile [BMB] (33.8 kg) obtained in Comparative Example 2(1) and anhydrous potassium carbonate (50.3 kg) was added to acetonitrile (312.2 kg) and the solution was heated (80-85 °C) for 5 hours under reflux. The reaction solution was cooled and insoluble materials were isolated. The solution was washed with acetonitrile (38 kg) and the filtrate was concentrated under reduced pressure to obtain the concentrate of methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate [BBN].

Comparative Example 2(3)

Production of methyl 2-[[(2'-cyanobiphenyl-4-yl]methyl]amino]-3-nitrobenzoate [MBN]

The concentrate (methyl 2-[N-t-butoxycarbonyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate [BBN]) obtained in Comparative Example 2(2), methanol (190 kg) and 35 % concentrated hydrochloric acid (104.0 kg) were mixed and the solution was stirred at 10 °C for 1 hour, and then stirred for 1-1.5 hours under reflux (67 °C). The reaction

Reference Example 6

Production of trioctyltin azide [TOTA]

Sodium azide (160 kg) was dissolved in deionized water (505 L) and the solution was cooled to 3-10 °C. To the solution was dropped trioctyltin chloride [TOTC] (847 kg) for 1-3 hours and the solution was stirred at 5-10 °C for about 2 hours. The reaction solution was extracted with methylene chloride (1822 kg, followed by 546 kg). The methylene chloride layer was washed with a mixture of deionized water (50 L) and 10 % sodium chloride solution (440 L) and concentrated under reduced pressure to give trioctyltin azide [TOTA].

Reference Example 7

Production of methyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate [MET]

A mixture of methyl 1-[(2'-cyanobiphenyl-4-yl)-methyl]-2-ethoxybenzimidazole-7-carboxylate [BEC] (228 kg) obtained in Reference Example 5, the residue containing trioctyltin azide [TOTA] obtained in Reference Example 6 and toluene (1148 L) was heated for about 40 hours under reflux (115-120 °C). The reaction solution was cooled and concentrated under reduced pressure. To the residue were added ethanol (764 kg) and sodium nitrite solution (135 kg/460 L) and the solution was adjusted to pH 4.5-5.5 with concentrated hydrochloric acid (about 224 kg). To the solution was added ethyl acetate (735 L) and the solution was adjusted to pH 0.5-1.5 with concentrated hydrochloric acid (about 100 L). To the solution was added hexane (1005 L) and the solution was adjusted to pH 3.5±0.5 with 4 % sodium hydroxide solution. The solution was cooled to 10 °C or less and stirred for 1 hour. The crystals were separated and washed with a mixture of ethyl acetate (106 L) and hexane (310 L), followed by hexane (410 L) to give wet MET (396.6 kg).

Reference Example 8

Production of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid [Compound A]

To the wet MET(369.6 kg) obtained in Reference Example 9, was added sodium hydroxide solution (73 kg/826 L) and the solution was stirred at 68-72 °C for 1-2 hours. The reaction solution was cooled and washed twice with methylene chloride (486 kg) and once with toluene (366 L). To the aqueous layer was added methanol (1437 L) and the solution was adjusted to pH 7.0±0.5 with concentrated hydrochloric acid (about 35 L). To the solution was added active charcoal (11 kg) and the solution was stirred for about 30 minutes. The active charcoal was filtered off and concentrated hydrochloric acid (about 20 L) was added to the solution until the solution became cloudy. The solution was stirred at 25±5 °C for about 1 hour, to which was added water (487 L), and the solution was adjusted to pH 3.5±0.3 with concentrated hydrochloric acid (about 85 L). The solution was stirred at 24-30 °C for about 30 minutes, to which was added water (687 L), and the solution was cooled to 10 °C or less and stirred for about 1 hour. The crystals were separated, washed with water (412 L) followed by acetone (427 L), crushed and dried to give 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid [Compound A] (200 kg, 82.0 %).

m.p. 183-185 °C
^{1}H-NMR (200MHz, DMSO-d_6) δ : 1.38 (3H, t), 4.58 (2H, q), 5.63 (2H, s), 6.97 (4H, q), 7.17 (1H, t), 7.47-7.68 (6H, m)
IR(KBr)cm^{-1}: 1710, 1550, 1480, 1430, 1280, 1240, 1040, 760

Reference Example 9

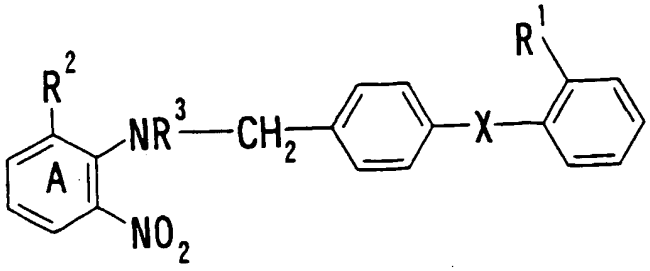
Production of 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid [Compound A(T)]

In methylene chloride (183 kg) was suspended 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid [Compound A] (480 kg) obtained in Reference Example 8. To the suspension was added triethylamine (13.8 kg) to dissolve Compound A. To the solution was added triphenylmethylchloride (34.9 kg) in methylene chloride solution (50 L) and the solution was heated for about 6 hours under reflux (40 °C). To the solution was added methylene chloride (273 kg) and the solution was allowed to stand at room temperature for one night. The reaction solution was heated at 30-35 °C, to which was added methanol (81.4 kg). To the solution was added water (205 kg) and the solution was adjusted to pH 3.1±+0.2 with 1N hydrochloric acid . The organic layer was separated and concentrated to 288 kg. The concentrate was stirred at room temperature for about 30 minutes, to which was dropped hexane (68 kg)

utes, and a part of the crystals was picked up to check the crystalline form by the X-ray powder diffraction. To the solution was added a mixture of acetone-pure water (3:1) (about 25 L), and the solution was cooled to 5±5 °C and stirred for about 1 hour. The separated crystals were separated, washed with a mixture of acetone-pure water (3:1) (about 25 L), dried and crushed to give crystals of (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate [Compound B] (23.0 kg, 93.0 %).

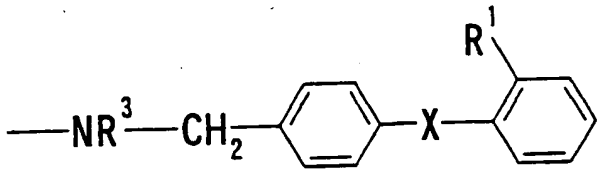
Claims

1. A method for producing an aminobenzene compound of the formula:



(IV)

wherein the ring A is a benzene ring which may have an optional substituent in addition to the group R^2, the nitro group and the group of the formula:

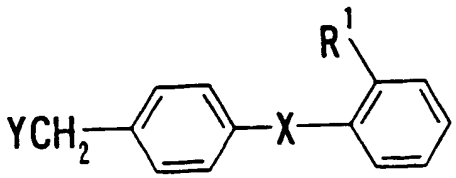


;

R^1 is a group capable of forming an anion or transformable thereinto;
R^2 is a group capable of forming an anion or transformable thereinto;
R^3 is an acyl group; and
X is a chemical bond or a spacer having a chain length of 1 to 2 atoms as the linear moiety between the adjoining phenylene group and phenyl group; or a salt thereof,

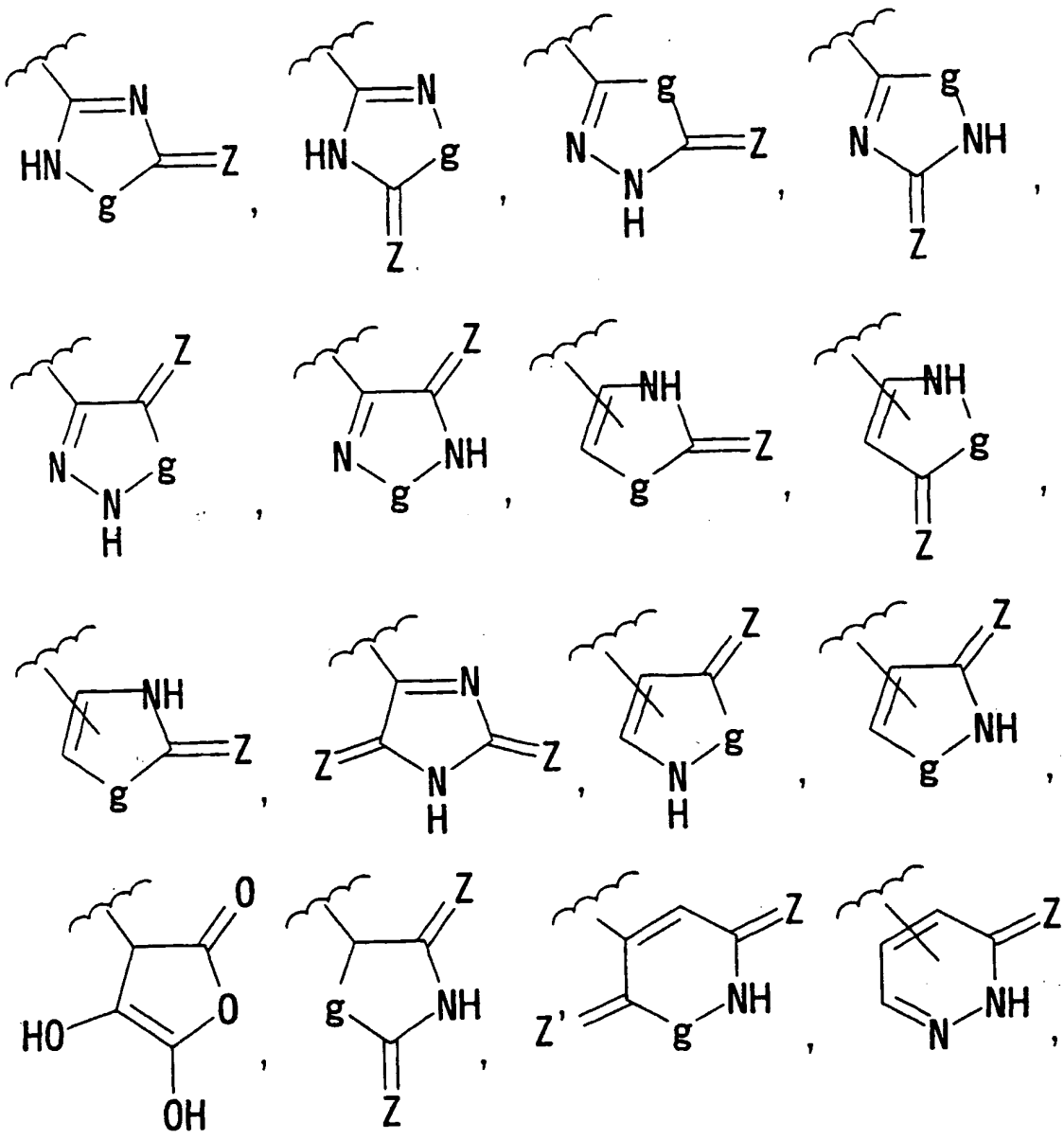
which comprises reacting a mixture containing

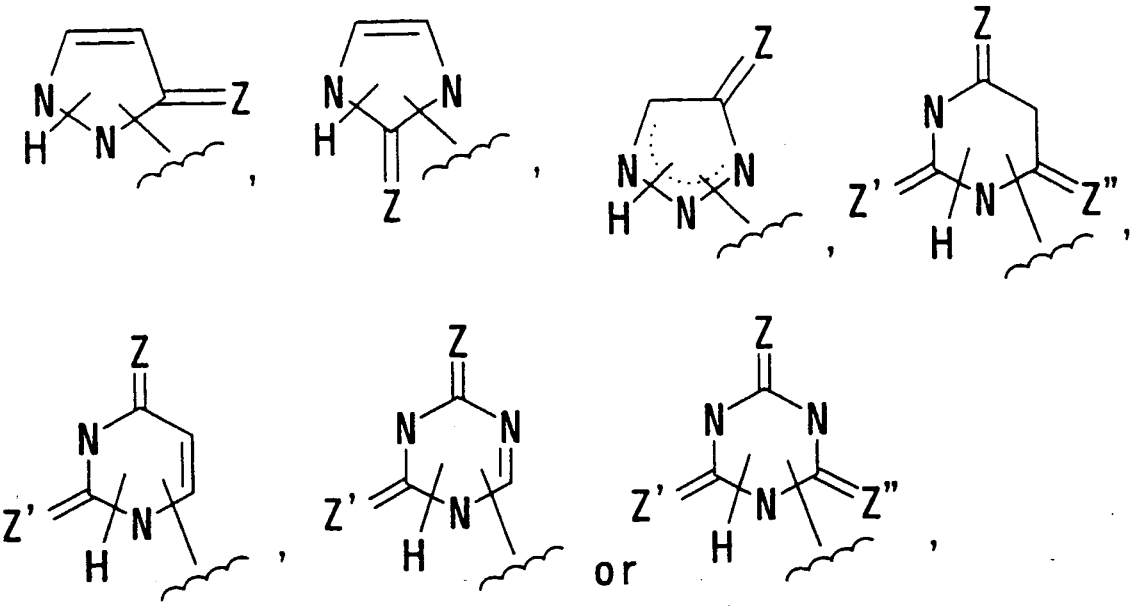
(i) a mono-halogeno compound of the formula:



(II)

wherein Y is a halogen atom and the other symbols are as defined above,
or a salt thereof and
(ii) a di-halogeno compound of the formula:

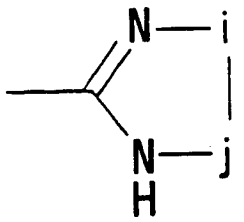




wherein g is $-CH_2-$, -NH-, -O- or -S(O)m-; >=Z, >=Z' and >= Z" are respectively a carbonyl group, a thiocarbonyl group or an optionally oxidized sulfur atom; and m is an integer of 0, 1 or 2, which may be protected by an optionally substituted lower (C_{1-4}) alkyl group or an acyl group and which may be substituted with an optionally substituted lower (C_{1-4}) alkyl group, a halogen atom, a nitro group, cyano, a lower (C_{1-4}) alkoxy group or an amino group optionally substituted with 1-2 lower (C_{1-4}) alkyl groups.

7. A method according to claim 5, wherein the heterocyclic group is an oxadiazolone ring, an oxadiazolothione ring or a thiadiazolone ring, which may be protected by an optionally substituted lower (C_{1-4}) alkyl group or an acyl group.

8. A method according to claim 5, wherein the heterocyclic group is a tetrazolyl group or a group of the formula:



wherein the symbol i is -O- or -S-, the symbol j is >C=O, >C=S or >S(O)m, and m is an integer of 0, 1 or 2.

9. A method according to any of claims 1 to 4, wherein R^1 is (1) carboxyl, tetrazolyl or 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl each of which may be protected with an optionally substituted lower (C_{1-4}) alkyl or acyl group, or (2) cyano or N-hydroxycarbamimidoyl.

10. A method according to any of claims 1 to 4, wherein R^1 is cyano.

11. A method according to any of claims 1 to 10, wherein X is a direct bond, a lower (C_{1-4}) alkylene in which the number of atoms composing the straight chain is 1 or 2, -CO-, -O-, -S-, -NH-, -CO-NH-, $-O-CH_2-$, $-S-CH_2-$ or -CH=CH-.

12. A method according to claim 11, wherein X is a direct bond.

13. A method according to any of claims 1 to 12, wherein the ring A has no substituent in addition to the group R^2, the

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EUROPEAN SEARCH REPORT

Application Number
EP 98 10 9211

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP 0 425 921 A (TAKEDA CHEMICAL INDUSTRIES LTD) 8 May 1991 * page 5 *	1	C07C253/30 C07C255/62
D,A	EP 0 459 136 A (TAKEDA CHEMICAL INDUSTRIES LTD) 4 December 1991 * page 7 *	1	
D,A	EP 0 553 879 A (TAKEDA CHEMICAL INDUSTRIES LTD) 4 August 1993 * the whole document *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	21 July 1998	Goetz, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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